AMENDMENTS TO THE CLAIMS

1-4. (**Canceled**)

5. (**Currently Amended**) An adzyme for enzymatically altering a substrate, wherein

said substrate is an insoluble protein-containing aggregate that comprises at least one polypeptide;

said ~~the~~ adzyme is ~~being~~ a cotranslational fusion protein encoded by a recombinant nucleic acid;

said adzyme comprises ~~, and comprising:~~ a protease domain that cleaves at least one peptide bond of said polypeptide of said substrate to produce one or more products, and a polypeptide targeting domain that reversibly binds with said polypeptide of ~~an address site on~~ said substrate, wherein the polypeptide bound by said targeting domain and the polypeptide cleaved by said protease domain are the same polypeptide;

said polypeptide targeting domain and said protease domain are discrete and heterologous with respect to each other; ~~,~~

said polypeptide targeting domain~~, when provided separately, binds to the substrate, and~~ is selected from at least one member of the group consisting of: an antibody or an antigen binding fragment thereof, a polypeptide comprising an antigen binding site, and a polypeptide comprising a protein scaffold. ~~, and a polypeptide that binds to the substrate,~~

~~said protease domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and~~

~~wherein the substrate is an insoluble protein-containing aggregate.~~

6. (**Canceled**)

7. (**Previously Presented**) The adzyme of claim 5, wherein the substrate is endogenous to a human patient.

8. (**Previously Presented**) The adzyme of claim 7, wherein the adzyme is effective against the substrate in the presence of physiological levels of human serum protein.

9. (**Previously Presented**) The adzyme of claim 8, wherein the human serum protein is human serum albumin.

10-25. (**Canceled**)

26. (**Previously Presented**) The adzyme of claim 5, wherein said fusion protein comprises a linker between said protease domain and said targeting domain.

27. (**Previously Presented**) The adzyme of claim 26, wherein said linker is an unstructured peptide.

28. (**Canceled**)

29. (**Previously Presented**) The adzyme of claim 27, wherein said linker comprises one or more repeats of Ser_4Gly (SEQ ID NO: 7) or $SerGly_4$ (SEQ ID NO: 8).

30. (**Canceled**)

31. (**Previously Presented**) The adzyme of claim 26, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting domain such that said adzyme is more active than said catalytic domain or targeting domain with respect to the reaction with said substrate.

32-36. (**Canceled**)

37. (**Previously Presented**) The adzyme of claim 5, wherein the substrate is produced by a cell.

38-47. (**Canceled**)

48. (**Previously Presented**) The adzyme of claim 5, wherein the substrate is an amyloid deposit or an atherosclerotic plaque.

49. (**Previously Presented**) The adzyme of claim 5, wherein the substrate is produced by a pathogen.

50. (**Previously Presented**) The adzyme of claim 49, wherein the pathogen is a protozoan, a fungus, a bacterium, or a virus.

51. (**Previously Presented**) The adzyme of claim 5, wherein the substrate comprises a prion protein.

52-55. (**Canceled**)

56. (**Withdrawn**) The adzyme of claim 5, wherein said protease is a zymogen.

57. (**Canceled**)

58. (**Previously Presented**) The adzyme of claim 5, wherein said adzyme is purified from a cell culture in the presence of a reversible protease inhibitor.

59-68. (**Canceled**)

69. (**Previously Presented**) The adzyme of claim 5, wherein the adzyme is resistant to autocatalysis by the protease domain at an adzyme concentration that is about equal to the concentration of adzyme in a solution to be administered to a subject.

70. (**Previously Presented**) The adzyme of claim 5, wherein said adzyme alters the half-life of the substrate *in vivo*.

71. (**Canceled**)

72. (**Previously Presented**) The adzyme of claim 5, wherein said adzyme alters the distribution of the substrate *in vivo*.

73. (**Canceled**)

74. (**Previously Presented**) The adzyme of claim 5, wherein said adzyme inhibits a biological activity of said substrate relative to said biological activity in the absence of said adzyme.

75. (**Canceled**)

76. (**Previously Presented**) The adzyme of claim 5, wherein said substrate binds a plurality of different molecules *in vivo*, and said adzyme alters the binding specificity of said substrate.

77. (**Canceled**)

78. (**Previously Presented**) The adzyme of claim 5, wherein said adzyme alters the interaction of said substrate with other molecules *in vivo*.

79-107. (**Canceled**)

108. (**Previously Presented**) The adzyme of claim 5, wherein the targeting domain is selected from the group consisting of a monoclonal antibody, an Fab and $F(ab)_2$, an scFv, a heavy chain variable region and a light chain variable region.

109. (**Canceled**)

110. (**Withdrawn**) The adzyme of claim 5, wherein said targeting domain is a soluble ligand binding portion of a receptor that binds to the substrate.

111-116. (**Canceled**)

117. (**Previously Presented**) The adzyme of claim 5, wherein the protease is selected from the group consisting of: MT1-MMP; MMP12; tryptase; MT2-MMP; elastase; MMP7; chymotrypsin; and trypsin.

118-126. (**Canceled**)

127. (**Previously Presented**) An adzyme preparation for therapeutic use in a human patient, the preparation comprising the adzyme of claim 5.

128. (**Original**) The adzyme preparation of claim 127, further comprising a pharmaceutically effective carrier.

129. (**Original**) The adzyme preparation of claim 127, wherein the adzyme preparation is formulated such that autocatalytic modification of the adzyme is inhibited.

130. (**Canceled**)

131. (**Previously Presented**) The adzyme preparation of claim 127, further comprising a reversible inhibitor of said protease.

132. (**Original**) The adzyme preparation of claim 131, wherein the reversible inhibitor is safe for administration to a human patient.

133. (**Original**) The adzyme preparation of claim 127, wherein said adzyme preparation is substantially pyrogen free.

134. (**Original**) The adzyme preparation of claim 127, wherein said adzyme preparation is packaged with instructions for administration to a patient.

135. (**Withdrawn**) A method of making a medicament for use in treating a disorder that is associated with an activity of the substrate of an adzyme of claim 5, the method comprising formulating the adzyme for administration to a human patient.

136. (**Canceled**)

137. (**Withdrawn**) A method of treating a disorder that is associated with an activity of the substrate of an adzyme of claim 5, the method comprising administering a therapeutically effective dose of the adzyme to a human patient in need thereof.

138-146. (**Canceled**)

147. (**Withdrawn**) A method for manufacturing an adzyme, the method comprising

a) culturing a cell comprising an expression vector comprising a nucleic acid encoding the adzyme of claim 5, in conditions that cause the cell to produce the adzyme; and

b) purifying the adzyme to substantial purity.

148-149. (**Canceled**)

150. (**Withdrawn**) The method of claim 147, wherein the purifying the adzyme to substantial purity includes the use of a reversible inhibitor that inhibits autocatalytic activity of the catalytic domain.

151-155. (**Canceled**)

156. (**Previously Presented**) The adzyme of claim 5, wherein the targeting moiety comprises a polypeptide or polypeptide complex.

157. (**Previously Presented**) The adzyme of claim 5, wherein the adzyme is resistant to autocatalysis.

158. (**Currently Amended**) An adzyme for enzymatically altering a substrate, wherein

said substrate is an insoluble protein-containing aggregate that comprises at least one polypeptide and is selected from an amyloid deposit or a substrate produced by a pathogen;

said ~~the~~ adzyme is ~~being~~ a cotranslational fusion protein encoded by a recombinant nucleic acid;

said adzyme comprises ~~, and comprising:~~ a protease domain that cleaves at least one peptide bond of said polypeptide of said substrate to produce one or more products, and a polypeptide targeting domain that reversibly binds with said polypeptide of ~~an address site on~~ said substrate ~~or with an address site on a second molecule that occurs in~~

~~functional proximity to the substrate~~, wherein the polypeptide bound by said targeting domain and the polypeptide cleaved by said protease domain are the same polypeptide;

said polypeptide targeting domain and said protease domain are discrete and heterologous with respect to each other; ~~,~~

said polypeptide targeting domain~~, when provided separately, binds to the substrate, and~~ is selected from at least one member of the group consisting of: an antibody or an antigen binding fragment thereof, a polypeptide comprising an antigen binding site, and a polypeptide comprising a protein scaffold. ~~, and a polypeptide that binds to the substrate,~~

~~said protease domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and~~

~~wherein the substrate is an insoluble protein-containing aggregate selected from an amyloid deposit or a substrate produced by a pathogen.~~

159. (**Previously Presented**) The adzyme of claim 158, wherein said fusion protein comprises a linker between said protease domain and said targeting domain.

160. (**Previously Presented**) The adzyme of claim 159, wherein said linker is an unstructured peptide.

161. (**Previously Presented**) The adzyme of claim 159, wherein said linker comprises one or more repeats of Ser_4Gly (SEQ ID NO: 7) or $SerGly_4$ (SEQ ID NO: 8).

162. (**Withdrawn**) A method for manufacturing an adzyme, the method comprising

a) culturing a cell comprising an expression vector comprising a nucleic acid encoding the adzyme of claim 158, in conditions that cause the cell to produce the adzyme; and

b) purifying the adzyme to substantial purity.

163. (**Withdrawn**) The method of claim 162, wherein the purifying the adzyme to substantial purity includes the use of a reversible inhibitor that inhibits autocatalytic activity of the catalytic domain.

164. (**New**) An adzyme for enzymatically altering a substrate polypeptide, wherein

said substrate polypeptide is a single polypeptide;

said adzyme is a cotranslational fusion protein encoded by a recombinant nucleic acid;

said adzyme comprises a protease domain that cleaves at least one peptide bond of said substrate polypeptide to produce one or more products, and a polypeptide targeting domain that reversibly binds with said substrate polypeptide;

said polypeptide targeting domain and said protease domain are discrete and heterologous with respect to each other;

said polypeptide targeting domain is selected from at least one member of the group consisting of: an antibody or an antigen binding fragment thereof, a polypeptide comprising an antigen binding site, and a polypeptide comprising a protein scaffold.

165. (**New**) An adzyme for enzymatically altering a substrate,

wherein said substrate is an insoluble protein-containing aggregate comprising at least one polypeptide;

said adzyme is a cotranslational fusion protein encoded by a recombinant nucleic acid;

said adzyme compries a protease domain that cleaves at least one peptide bond of said polypeptide of said substrate to produce one or more products, and a polypeptide targeting domain that reversibly binds with said polypeptide of said substrate, wherein the polypeptide bound by said targeting domain and the polypeptide cleaved by said protease domain are the same polypeptide, and a linker between said protease and targeting domains;

said polypeptide targeting domain and said protease domain are discrete and heterologous with respect to each other;

said polypeptide targeting domain is selected from at least one member of the group consisting of: an antibody or an antigen binding fragment thereof, a polypeptide comprising an antigen binding site, and a polypeptide comprising a protein scaffold;

said protease domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and is selected from prethrombin, thrombin, MT1-MMP, MMP12, tryptase, MT2-MMP, elastase, and MMP7;

said linker is selected to provide steric geometry between said catalytic domain and said targeting domain such that said adzyme is more active than said catalytic domain or targeting domain with respect to the reaction with said substrate.

166. (**New**) The adzyme of claim 165, wherein the linker comprises at least one of a pentapeptide GGGGS, a AAA sequence, an unstructured peptide, Ser_4Gly (SEQ ID NO: 7) or $SerGly_4$ (SEQ ID NO: 8).

167. (**New**) The adzyme of claim 165, wherein said adzyme inhibits the bioactivity of TNFα and the protease domain is selected from MT1-MMP, MMP12, tryptase, MT2-MMP, elastase, and MMP7.